

REMARKS

Claims 16-21, 31-36, 38, 44-58, 69-76, 78-92, 94-97, and 99-174 are pending in the application, claims 77, 93, and 98 having been cancelled and new claims 135-174 added by the above amendment. Claims 47 and 54 are amended to specify that less than 12 ppm NO₂ is present in the NO-containing gas, a limitation derived from claim 104. The limitations added to claims 76, 87, 92, and 97 are found in (cancelled) claims 77, 93, and 98. New claims 135-139 and 153-158 are derived from claims 76, 78-82, 104, and 105. New claims 140-144 and 159-164 are derived from claims 85, 87-91, 104, and 105. New claims 145-147 and 165-168 are derived from claims 92, 94-96, 104, and 105. New claims 148-152 and 169-174 are derived from claims 97 and 99-105. The remaining amendments are merely editorial in nature. None of the amendments add new matter.

In the Office Action dated November 19, 1996, the Examiner allowed claims 115-119, 127-129, and 132, and said that claims 38, 45, 74, 77, 78, 93, 94, 98, and 99 would be allowable if rewritten in independent form. The remaining claims were rejected on various grounds, discussed below.

35 USC §112, ¶2

The Examiner rejected claims 45, 74, 83-86, 104-114, 120-126, 130, 131, 133, and 134 for indefiniteness, suggesting particular amendments that would resolve the issues. Applicants thank the Examiner for the extensive and detailed recommendations, most of which have been incorporated into the above amendments largely as suggested. In a few cases, Applicants have followed the spirit of the recommended changes but have worded the amendments somewhat differently than suggested. In addition, the above amendment revises some claims (including some allowed claims) that were not rejected for indefiniteness but which included language objected to as indefinite in other claims. In view of these amendments, withdrawal of the rejection for indefiniteness is requested.

35 USC §103(a)

Claims 16-21, 31-36, 44, and 46 were rejected as obvious over Thompson et al. ('305). Applicants note that this patent is prior art as of its filing date (November 26, 1990) under 35 USC §102(e). The present application has a priority date of December 5, 1990. Submitted herewith is a Declaration under 37 CFR §1.131 attesting to the fact that the invention embodied in claims 16-21 and 31-36 was conceived by Applicants in the United States by November 21, 1990, which is just prior to the 102(e) date of the Thompson et al. patent. This Declaration and a Supplemental Declaration also filed herewith provide further evidence, including attorney billing records, that prove that the draft application was diligently completed and filed by December 5, 1990. In view of this evidence, Applicants have established that the date of invention of these claims clearly precedes Thompson's filing date, and so Thompson is not citable as 102(e) prior art against these claims. Withdrawal of the rejection with respect to these claims is therefore requested.

Claims 44 and 46 were also rejected as obvious over Thompson et al. These claims cover methods of delivering an NO-releasing compound via inhalation, specifically for the purpose of improving gas exchange in the lungs. Gas exchange is a problem in patients suffering from a condition such as pneumonia in which part of the airspace of the lung is functioning essentially normally and part is filled with liquid or collapsed. When the airspace of the lung is collapsed or filled with liquid, air cannot enter the alveoli, the tiny air sacs of the lung where gas exchange between the air and the blood in nearby blood vessels takes place. Because of the absence of air in the malfunctioning, fluid-filled region of the lung, blood which continues to course through the blood vessels in the malfunctioning region cannot pick up oxygen and discard CO₂ as it normally would. Ideally, one would want to minimize the amount of blood which flows through the blood vessels of this region, and maximize the flow of blood through the part of the lung in which the air is entering and exiting in a normal fashion (i.e.,

the "ventilated" region), so as to permit as much of the blood as possible to unload its CO₂ and pick up oxygen. This goal is addressed by the invention claimed in claims 44 and 45. The inhaled particles or droplets of NO-releasing compound, or the NO molecules released therefrom, are carried into the airspace of the lung on the inhaled air. Therefore, they will enter only the areas where inhaled air can reach: i.e., the ventilated airways of the lung. Thus, the method of the invention has the very desirable result of ensuring that only those blood vessels which serve the ventilated region of the lung will be exposed to the vasodilating effects of NO and the concomitant increased blood flow. The blood vessels in the malfunctioning, fluid-filled region receive little or no NO and so remain constricted, which means they have a lesser blood flow. This redistribution of blood flow in the lung following NO treatment has been demonstrated to result in an improved degree of gas exchange in the patient, in marked contrast to the results seen when such a patient is treated with a standard systemic type of vasodilator that nonspecifically and harmfully dilates all of the blood vessels in the lung.

Nowhere does Thompson et al. discuss these concepts. The fact that this reference discusses sublingual, transdermal, rectal, vaginal, intravenous, and oral delivery as well as delivery via inhalation suggests that the intent is to produce systemic vasodilation rather than pulmonary-specific effects. While systemic vasodilators have in the past been used occasionally to treat pulmonary hypertension (particularly prior to development of the superior inhaled NO methods of the invention), they tend to act indiscriminately on blood vessels throughout the body. Thus, with such vasodilators, there is no discrimination between those blood vessels which serve ventilated airways of the lung, and those which serve blocked airways. Thompson does not suggest, and provides no basis to suggest, that any of the vasodilators disclosed in that reference could be used so to discriminate: that is, to treat a condition in which improved gas exchange (i.e., increased blood flow solely in the

ventilated regions of the lung) might be beneficial. A compound generally useful to reduce hypertension, such as those described in Thompson, is not useful to improve gas exchange unless it is capable of discriminating between ventilated and nonventilated regions of the lung. The prior art taught that a patient in need of improved gas exchange should not be treated with a systemic vasodilator, as it will worsen the patient's condition. Thompson does not address this issue. Because he gives no reason to believe that inhalation of his systemic vasodilators would produce the discrimination effect essential for a patient specifically in need of improved gas exchange, he provides no motivation to identify and treat such a patient. The latter are positive limitations of claims 44 and 46, and cannot be read out of the claims. Thus, claims 44 and 46 are not obvious in view of Thompson et al.

If the Examiner believes that the limitations concerning identifying and treating a patient in need of improved gas exchange are somehow inherent to the teachings of Thompson et al. on the general subject of treatment of pulmonary hypertension, then these limitations would be similarly inherent to the invention conceived by Applicants prior to the filing date of Thompson et al., as evidenced by the Declarations submitted herewith. Based on that assumption, the Declarations would be effective in swearing behind Thompson et al. with respect to claims 44 and 46. Thus, either way, the rejection of these claims should be withdrawn.

Claims 47-58 are rejected as obvious over Weinstein ('419) in view of Higenbottam et al. and (solely in the case of claim 57) further in view of Sackner et al. Applicants have amended independent claims 47 and 54 to specify that the NO-containing gas contains less than 12 ppm NO₂. Since none of the cited references says anything about NO₂, nor provides any reason to believe that high levels of NO₂ would be detrimental and should be avoided, the claims as amended cannot be said to be obvious. Withdrawal of the rejection is therefore requested.

Claims 69-73 and 75 are rejected as obvious over Thompson et al., further in view of Weinstein et al. As discussed in the enclosed Declaration under 37 CFR §1.131, the invention embodied in these claims was generally disclosed in the November 21, 1990, draft application on page 10, line 26 through page 11, line 6, and was claimed in claims 32-35 of that draft application. This Declaration, together with the accompanying Supplementary Declaration, proves conception of the invention in the United States prior to the Thompson et al. filing date, together with diligent constructive reduction to practice. Thus, Thompson et al. is not citable as prior art against claims 69-73 and 75 of the present application. The rejection should therefore be withdrawn.

Claims 76, 79-82, 92, 95-97, and 100-103 are rejected as obvious over the combination of Walstrom et al. ('138) and Higenbottom et al. Applicants have amended the independent claims (claims 76, 92, and 97) to include a limitation concerning an NO₂ scavenger. The Examiner indicated on page 4 of the Office Action that such a limitation would render claims 76 and 92 allowable, and it is believed that the same reasoning applies to claim 97 (since claim 98, which contains this limitation, was "objected to" and not rejected outright). Thus, withdrawal of the rejection in view of the amendments to the claims is respectfully requested.

Applicants note that new claims 135-139 and 145-152 differ from amended claims 76, 79-82, 92, 95-97, and 100-103, respectively, solely in that these new claims replace the scavenger limitation with a limitation concerning an NO₂ analyzer. Inclusion of the analyzer limitation is said by the Examiner on page 4 of the Office Action to render claim 76 allowable; it is believed that the same reasoning would also apply to claims 92 and 97, and therefore to the new claims based upon claims 76, 92, 97, and the claims dependent therefrom.

Claims 87-91 were rejected as obvious over the combination of Walstrom et al., Higenbottam et al., and Gauthier et al. ('991). Applicants have amended claim 87 to include a

limitation concerning an NO₂ scavenger, and have added a new set of claims (claims 140 to 144) derived from claims 87-91 but including a limitation regarding an NO₂ analyzer. Since none of the cited references provides any motivation to include an NO₂ scavenger or analyzer in the apparatus, claims 87-91 and new claims 140 to 144 are patentable over the cited references. Withdrawal of the rejection is requested.

New claims 153-174 are modeled on claims 76, 85, 92, and 97, and claims dependent thereon, with added limitations concerning NO₂ concentration. Since nothing about limiting NO₂ concentration was taught in any of the prior art, these claims should be deemed patentable.

Applicant submits that all of the claims are now in condition for allowance, which action is requested. Filed herewith is a check in payment of the excess claims fees required by the above amendments, and a Petition for Automatic Extension with the required fee. Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date:

March 19, 1997

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